interactions and strategic relationships between the societies. The MoU will facilitate collaboration across the ocean on e.g. Joint Task Groups, Scientific meetings and Education. The development of reports (e.g. AAPM task group reports, professional guidelines, etc.) should seek collaboration between the two societies where appropriate and feasible. Such collaboration could be achieved by inviting joint membership on appropriate drafting task groups by the initiating society. Both societies have now Standard Operating Procedures (SOP) available for development of guidelines, which gives a good structure for initiating international guidelines and securing high quality reviews - representing both Europe and North America – in upcoming guidelines.

Proffered Papers: Radiobiology 5: Imaging and molecular biomarkers in radiation oncology

OC-0526

Noninvasive imaging of the PD-1/PD-L1 checkpoint in naïve mice and after combined radioimmunotherapy

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Purpose or Objective: There is increasing evidence that antibodies blocking the PD-1 checkpoint (either anti-PD-1 or anti-PD-L1) dramatically increase in-field anti-tumor responses to ionizing radiation and enhance abscopal effects on non-irradiated metastases. Here, we developed PET tracers based on therapeutic surrogate antibodies that enable to non-invasively visualize not only the PD-1 and PD-L1 expression in mice but also the biodistribution of the surrogate checkpoint-blocking antibodies.

Material and Methods: Two novel PET tracers were developed by conjugation of anti-murine PD-1 and PD-L1 surrogate checkpoint-blocking antibodies with the chelator NOTA and labeling with the radioisotope 64Cu. Non-invasive PET imaging was performed on naïve and tumor-bearing mice. Mice bearing s.c. B16 melanomas were treated with hypofractionated radiation therapy (hRT) using two fractions of 12 Gy in combination with CTLA-4 checkpoint blockade several days before PET imaging. PD-1 or PD-L1 knockout mice and PD-L1-deficient B16 cells generated using the CRISPR/Cas technology served as specificity controls.

Results: The newly developed PD-1 and PD-L1 PET tracers allowed the highly specific and high-resolution imaging of PD-1 and PD-L1 expression and of the biodistribution of the two therapeutic antibodies in both naïve and tumor-bearing mice treated with hRT and CTLA-4 checkpoint blockade. Imaging of the respective knockout mice, blocking experiments with an excess amount of unlabeled antibodies, and the analysis of animals bearing both wild-type B16 melanomas and PD-L1-CRISPR knockout melanomas demonstrated the high specificity of the two newly developed PET tracers. The in vivo imaging data were confirmed by ex vivo biodistribution analyses. The targets of the PET tracer antibodies were verified by ex vivo flow cytometric analyses of tumor single-cell suspensions and cell suspensions of secondary lymphoid and other organs. Interestingly, visualization of immune-related adverse events was also possible.

Conclusion: We developed two innovative PET tracers that allow imaging the expression of the receptor/ligand pair of the important PD-1 checkpoint and the biodistribution of surrogate checkpoint-blocking antibodies in fully immunocompetent mice. This technology also enabled whole-body pictures of combination radio/immunotherapies.

OC-0527

Monitoring mitochondrial complex-I using novel PET probe allows early detection of radiosensitivity

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Purpose or Objective: Objectives: Aerobic glycolysis is the main pathway of energy production in tumors (Warburg effect), and ionizing radiation is reported to switch this to mitochondrial oxidative phosphorylation. We developed a novel PET probe,18F-2-tert-butyl-4-chloro-5- {6-[2-(2-fluoro-ethoxy)-ethoxy]-pyridin-3-ylmethoxy}-2H-pyridazin-3-one (18F-BCPP-EF), for imaging mitochondrial complex I (MC-I) activity. In this study, early detection of tumor radiotherapeutic effect was evaluated using 18F-BCPP-EF and compared with 18F-FDG and apoptosis index.

Material and Methods: Methods: Tumor uptake of 18F-BCPP-EF or 18F-FDG was examined in C3H/HeN mice inoculated with murine squamous cell carcinoma SCCVII after a single dose of x-ray irradiation, 0, 6, 15, or 30 Gy. Apoptosis incidence was determined by TUNEL staining in excised tumor tissue.

Results: Results: Tumor growth suppression was dose-dependent; tumor grew 10 fold (0 Gy), 5 fold (6 Gy), 2 fold (15 Gy), and reduced to half in its volume (30 Gy) 14 days after treatment. 18F-BCPP-EF uptake was significantly increased as early as 2 days (15 Gy) or 3 days (30 Gy) after irradiation, at time points when tumor size or apoptosis index showed no difference among radiation doses. In contrast, 18F-FDG uptake was initially increased dose-dependently, remained elevated, and eventually decreased 10 days after 30 Gy when tumor size was already reduced. Apoptosis index was increased after irradiation but failed to correlate with tumor response. The uptakes of 18F-BCPP-EF and 18F-FDG, as well as AI, were plotted against Tvol on day 14 as surrogate of radiotherapeutic effect. Highly significant negative correlations were observed between the uptake of 18F-BCPP-EF and Tvol on day 14, as early as on day 2, and on each day up to day 7, and in all days combined. In contrast, between tumor uptake of 18F-FDG and Tvol on day 14, there was a significant negative correlation on day 2 and positive correlations on day 10 and on day 14, with no correlation in all days combined.

Conclusion: Conclusion: Tumor uptake of 18F-BCPP-EF was increased dose-dependently early after irradiation when 18F-FDG uptake and apoptosis index remained elevated regardless of radiation doses or its efficacy. The results suggest that 18F-BCPP-EF is a promising “positive” MC-I imaging PET probe for early detection of adequacy of tumor radiotherapy.

OC-0528

Modelling tissue radiosensitivity and PET hypoxia image contrast in acute and chronic hypoxia

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Purpose or Objective: PET imaging studies with the hypoxia tracer 18F-MISO typically show a heterogeneous distribution within the tumour, and regions of high uptake have been proposed as targets for dose painting. However, there is no widely-accepted method to determine dose prescriptions from hypoxia imaging. Oxygen diffusion distances in tissue (~100 μm) are smaller than the PET resolution (~4 mm) so a range of radiosensitivities may exist within each voxel. Furthermore, the perfused vasculature is not constant over